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DYSPEPTIC AND OTHER REFERRED SYMPTOMS ASSOCIATED WITH DISEASE OF THE GALL BLADDER AND OF THE APPENDIX.

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BY

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By referred symptoms is meant those that do not at once suggest local disease of the organ really responsible or that are remote in point of place; they might be described as masked or, as they are often the first manifestations of disease, inaugural, or as larval or *fruste*.

The discussion of this subject has its difficulties; to consider separately the gall bladder and the referred symptoms caused by its disease and then appendicitis and its referred symptoms might be the simplest course; but as this would lead to some tedious repetition it appears advisable to take the symptoms and to refer incidentally to their causation. Most of the infective complications of gall bladder and appendix disease, such as the various forms of hepatic suppuration, empyema and fistulae, and intestinal obstruction due to adhesions, bands or gall stones, will not be mentioned. Except when specially stated, the disease of the gall bladder and appendix is not acute but either the result of a past attack of acute inflammation, such as fibrosis, adhesions or calculi, or a recurrent or chronic inflammation. Further, it may be pointed out that what we commonly call a "chronic appendix" is more often the result of a past attack than a progressive and chronic inflammatory process.

Mechanism of the Production of Symptoms.

The question how morbid changes in the gall bladder and appendix induce symptoms in other viscera and distant parts will be touched on in connexion with these manifestations, but the various mechanisms that may be at work in different cases may be tabulated here as (1) Reflex, (2) Mechanical, (3) Toxic, (4) Infective.

1. *Reflex.*—Irritation in the appendix or gall bladder may cause hypertonus of the stomach and spasm of, or failure to relax on the part of, the pyloric or ileo-caecal sphincter, leading to gastric or ileal stasis and so to excess of acid or to toxaemia. Vigorous contraction of the stomach extending to the pylorus has been watched by Moynihan, during the course of laparotomy on patients with appendix dyspepsia, and Hurst[9] has seen visible spasm of the middle of the stomach when the appendix is manipulated under the *x*-rays. The pyloric spasm or want of relaxation of the pylorus has been regarded as a protective mechanism. In the case of chronic appendicitis failure of relaxation of the ileo-caecal sphincter is thought by Hurst to be commoner than spasm. Caecal stasis from inhibition of peristalsis or from enterospasm (spastic constipation) may be due to chronic appendicitis; when situated in the pelvis a chronically inflamed appendix may reflexly inhibit defaecation (dyschezia, Hurst[10]). Appendicitis may reflexly lead to increased frequency or inhibition of micturition through an irritated focus in the spinal cord (Mackenzie); and chronic irritation of the appendix may be responsible for cardiac irregularities.

The reflex pain in the epigastrium, which is so common in appendix and gall-bladder dyspepsia, has given rise to some discussion; Mackenzie maintains that it is in the peripheral terminations of the sixth and seventh dorsal nerves in the abdominal wall, and that this depends on the irritated focus in the spinal cord, whereas Hurst[11] argues that the pain is visceral, in the pyloric end of the stomach, and due to the peristalsis. They both, however, agree that the epigastric tenderness is due, not to pressure on the stomach, but to the irritated focus in the spinal cord which causes an exaggerated sensory effect when the skin, and especially the muscles and the underlying subperitoneal tissues, are pressed on. The referred cutaneous pain in gall-bladder disease may occasionally spread to the top of the right shoulder, and extend down the outside of the arm, so that patients may for years be treated for "neuritis" until the passage of a gall stone at once brings relief (Mackenzie).

Very often the appendix when removed shows little naked-eye change to correspond with the prominent symptoms that then disappear; microscopic examination may be necessary to reveal the evidence of past inflammation in its walls, especially fibrosis in the submucous coat, and often, as I have seen in many sections, the changes are very slight. The ganglion cells of Auerbach and Meissner's plexuses have been found to show degeneration (Pfeiffer). Stimuli generated in the appendix travel by the sympathetic to the spinal cord, and by constant repetition give rise to a persistent irritable focus in the spinal cord, and so to a reflex extension of impulses. In women the right ovary and tube are very often matted together with the appendix, infection readily passing from one to the other. Ovarian and uterine dyspepsia, analogous to those now under consideration, have been described.

2. *Mechanical.*—Pericholecystitic adhesions may embarrass the movements of the stomach, interfere with the passage of food through the pylorus, or even lead to an hour-glass stomach. Though often the legacy left by cholecystitis, these adhesions may be due to duodenal or gastric ulcer. Peri-appendicular adhesions may cause intestinal stasis and so toxaemia, and the same result, only in a more marked degree, may be produced by an appendix adherent across the lower part of the ileum. In some cases adhesions about the appendix or the gall bladder may possibly alter the radiation of pain; adhesions around an inflamed gall bladder have been thought to cause left-sided pain, and adhesions between an inflamed gall bladder and the peritoneal coat of the appendix to explain the pain referred to the right iliac fossa (Tripier and Paviot).

3. *Toxic.*—Absorption of bacterial toxins from the gall bladder or appendix may set up general toxaemia, cause myocarditis, and damage the mucous membrane of the stomach and intestines, thus giving rise to haemorrhage. Toxic absorption from the inside of the organ is probably more often an important factor in the case of the gall bladder than of the appendix.

4. *Infective.*—Micro-organisms from the appendix or gall bladder may infect the kidneys, especially the right. Infection of the gall bladder is prone to spread to the pancreas, and local thrombo-phlebitis of branches of the iliac veins, secondary to appendicitis, may give rise to small pulmonary emboli and pleurisy; malignant endocarditis has been found to be associated with gall-bladder infection (Leva collected nine cases as long ago as 1892) and with appendicitis. As is well known, inflammation of the appendix and gall bladder are often associated; although the true relations of the two infections may vary, it seems probable that most commonly the appendix is the earlier affected and that from this focus the gall bladder becomes infected. The changes left in the appendix may be comparatively slight while there is considerable cholecystitis.

Dyspepsia.

The general recognition that disease of these two appendages of the alimentary canal may produce definite symptoms of gastric and duodenal disorder with few or no localizing symptoms is comparatively recent and is due to the observations on "the pathology of the living" (W. J. Mayo, Moynihan, Paterson, S. Fenwick); though had abdominal surgery been active in his time there can be little doubt that John Hilton would have expanded his conclusions on "sympathetic pains on the surface of the body connected with derangements of the internal viscera," and would have laid stress on the connexion between reflection of pain from the gall bladder to the stomach and duodenum on the one hand and the origin of the hepatic diverticulum from the foregut on the other.

As the dyspeptic symptoms in a certain number of cases depend on an organic lesion, resist symptomatic treatment,

but yield to operative interference, the term "surgical dyspepsia" has arisen.

This attractive explanation, however, must not lead to the conclusion that dyspepsia is always, or, indeed, usually, due to an organic cause, and that the short cut to a cure is by way of the knife. A high estimate, at least for a physician, is that of M. J. Lichty, among whose 1,500 patients with gastro-intestinal disorders 600, or 40 per cent., were found at operation to have disease of the gall bladder or appendix. It is, moreover, important to consider how far medicine can re-assert its position by in its turn preventing infection of the gall bladder and appendix. With regard to the gall bladder we know that cholecystitis is due to various foci of infection: from the vermiform appendix, from the intestines, particularly in enteric fever, from the stomach and teeth, and from the tonsils by the blood stream; for Rosenow and Brown have shown the great frequency of haemolytic streptococci in inflamed gall bladders, argue that *B. coli*, formerly considered as one of the two commonest causal organisms of cholecystitis, is often a secondary invader, and from experimental observation believe that these streptocccci in the tonsils have a special tendency to settle down in the gall bladder. The etiology of appendicitis has been much debated; probably several causes are at work; but the elimination of septic foci in the mouth, tonsils, and nasopharynx, the supervision of food supplies, and early attention to signs of intestinal infection and constipation would diminish the frequency of this surgical disease. In connexion with the prevention of tonsillitis it is appropriate to refer here to Dr. G. I. T. Stewart's observations showing the causal relation of bad teeth to inflammation of the tonsils.

Gall-bladder dyspepsia is sometimes spoken of as the result of gall stones rather to the exclusion of cholecystitis, whereas a broader view holds the field as regards appendix dyspepsia, which is ascribed to appendicitis, and not solely to the faecal concretions. The correct view is that in the main the cholecystitis causes both the symptoms and the gall stones. It is of course true that single cholesterin calculi may form without any antecedent inflammation of the gall bladder, though they may subsequently favour the occurrence of cholecystitis. These calculi are much less common than those due to cholecystitis, and, I believe, may form an exception to Sir Berkeley Moynihan's dictum that gall stones always cause symptoms.

The evidence that referred dyspepsia is due to disease of the appendix or gall bladder rests on the disappearance of the symptoms after removal of a chronic inflamed appendix or gall bladder, and is analogous to the familiar relief of headache by removal of a decayed tooth. Cases not relieved by gastro-enterostomy have subsequently been cured by appendicectomy, and it has been urged that no laparotomy for disease of the stomach or duodenum, especially if no obvious disease in these organs be found, is complete without examination of the gall bladder and appendix. It was noted by Soltau Fenwick that patients with a peculiar

form of gastric hypersecretion were prone to die from appendicitis, the real explanation apparently being that the hypersecretion was due to latent appendicitis which subsequently flared up. The diagnosis of gall bladder or appendix disease as the cause of dyspepsia in a given case may be very difficult; in both instances the primary lesion may be latent, there may be an absence of any history of an acute abdominal attack, and there may be no local tenderness over the gall bladder or appendix.

The dyspeptic symptoms associated with chronic disease of the gall bladder and appendix, which are commoner in women, show considerable variation, and it is very doubtful if any differential diagnosis as to which organ is primarily at fault can be made on the characters of the subjective manifestations only. Pain and tenderness on pressure in the epigastrium and flatulence are the most constant symptoms; the pain may be persistent, but is often at once made worse by food; or it may come on after an interval of hours, as in duodenal ulcer; possibly the pain directly after a meal in cases of cholecystitis or gall stones may be caused by vigorous contractions in the gall bladder as well as in the stomach. Heartburn is common, and vomiting may follow. The symptoms are often of long duration, and their obstinate resistance to remedies, such as bismuth, alkalis and food, that relieve ordinary indigestion, is a prominent feature. The prolonged pain and toxaemia, especially in cases with appendicitic adhesions, may induce neurasthenia and recurrent headaches. The condition of the gastric juice varies; there may be hyperchlorhydria, a normal or a much diminished amount of hydrochloric acid. Among 156 cases of gall-bladder disease, J. A. Lichty found that 84, or 54 per cent., showed hyperchlorhydria; 41, or 26 per cent., a normal; and 31, or 20 per cent., a diminished amount of HCl. Among Sherren's 20 cases of gall-bladder disease there was an absence of free HCl in 16.

There is a similar variation in appendix dyspepsia, and Fenwick considers that the condition of the appendix is an important determining factor; when there is active irritation, such as an enterolith or ulceration, hyperchlorhydria results, whereas with a merely thickened, adherent, or kinked appendix the symptoms are those of chronic gastritis with diminution or absence of HCl. He regards the hypersecretion as reflex, but there is the alternative view that spasm, or failure to relax on the part, of the pylorus leads to retention of food and accumulation of HCl. In a comparatively small number of cases there is haematemesis, which may be considerable and suggest gastric or duodenal ulcer. In my limited experience this has seemed less rare in appendix than in gall-bladder dyspepsia, but in a large series of cases operated upon in the Mayo clinic gastric haemorrhage and symptoms were present in 5 per cent. of gall-bladder infections and in 2 per cent. of appendicitis cases (Crispin). It is tempting to regard the haemorrhage as due to toxaemia, but the source of the poison is not always obvious, as the appendix may be

merely obliterated. It is true that Paterson and others ascribe the symptoms of appendix dyspepsia to toxaemia due to intestinal stasis, and on this hypothesis an exacerbation in the intestinal toxaemia might be postulated as the exciting cause of haematemesis. But considerable gastro-intestinal haemorrhage is rare in acute appendicitis in which the toxaemia is so much more obvious. It is somewhat fanciful to imagine that there is sufficient reflex dilatation of the vessels in the gastric mucosa to produce weeping, but this is perhaps suggested by the peritoneal flush over the pylorus in these cases of appendix dyspepsia. Soltau Fenwick's explanation of gastric haemorrhage is probably more satisfactory—namely, that as a result of long-continued exposure to gastric juice with two to five times the normal percentage of free hydrochloric acid the gastric mucous membrane becomes inflamed, acutely congested, and shows haemorrhagic erosions. In some instances a gastric or duodenal ulcer is associated with appendicitis or gall-bladder disease. Among 1,078 cases of gastric and duodenal ulcer at the Mayo clinic 40 per cent. showed disease of the appendix and 9.7 per cent. disease of the gall bladder (Eusterman). These figures perhaps explain my impression that haematemesis is less rare in appendix than in gall-bladder dyspepsia. In rare cases gastro-intestinal haemorrhage may be due to ulceration of the gall bladder or of the ampulla of Vater when a gall stone is impacted there, but in the latter instance the symptoms would be those of intermittent hepatic fever.

Diagnosis.

The differential diagnosis of appendix and gall-bladder dyspepsia from gastric and duodenal ulcer presents considerable difficulties, but an *x*-ray bismuth or barium meal may give valuable assistance in providing the positive evidence of gastric or duodenal ulcer on the one hand, or of appendix or gall-bladder disease on the other. Hurst[9] has tabulated the *x*-ray results in favour of the presence of a chronic lesion of the appendix, and points out that the tenderness of the appendix—the most important sign—may be missed without the guidance of *x*-rays, as the organ may be displaced when pressure is applied; other signs are those of adhesions, ileal and caecal stasis, and though hypertonus of the stomach, which empties itself with abnormal rapidity, may be present, this is both much less frequent and less well marked than in duodenal ulcer, the spasm due to chronic appendicitis being more commonly in the middle of the stomach. From careful examination of a large number of cases Spriggs finds that the following indications of chronic disease—namely, partial filling of and stasis of barium in the appendix, constrictions, dilatations, and concretions—can be demonstrated by the *x*-rays. Adhesions around the gall bladder are characterized by a high position of the stomach, displacement of the pylorus to the right, distortion of the duodenal cap and of the hepatic flexure of the colon, and retention of food in the stomach for six to eight hours.

Opinion differs as to the value of *x*-rays in the detection of gall stones; some American skiagraphists claim that 75 per cent. of gall stones can be thus diagnosed, and Pancoast and Pfahler regard 50 per cent. as a conservative estimate.

Turning to the other means of diagnosis, the pain of gastric ulcer is relieved by food and by alkalis, and in duodenal ulcer there are usually periods of complete freedom from symptoms and hyperchlorhydria; in both these conditions occult blood in the faeces is much more likely to be present than it is in the referred dyspepsias. In favour of an appendicular origin are radiation of pain towards the right iliac fossa, with local tenderness there or on rectal examination, and Bastedo's sign—namely, localized pain and tenderness on pressure in the right iliac fossa on inflation of the colon. Deep tenderness to the right of the spine between the seventh and eleventh ribs is regarded as pathognomonic of pericholecystitic adhesions by Friedman, who considers it more valuable than *x*-rays. The tenderness has been ascribed to extension of inflammation to the chest wall so as to set up a mild neuritis.

It must of course be borné in mind that both the appendix and the gall bladder may be diseased, and that removal of one may not cure the symptoms. A few words may be said about the way in which disease of the gall bladder and appendix may imitate each other. An elongated gall bladder with a Riedel's lobe or peritoneal adhesions between the two organs may explain why in some cases of cholecystitis a diagnosis of appendicitis is corrected only at laparotomy. The converse mistake is less common, but may be due to an appendicitis close to the right lobe of the liver so that it becomes adherent to the gall bladder, or to other less obvious causes. In this connexion the following case is interesting.

A man aged 32 years had jaundice when 14 years of age, and since then had had repeated attacks of jaundice, much flatulence, and general ill health. Two months before I saw him he had had an acute abdominal attack regarded as appendicitis, and was much jaundiced. When seen there was tenderness over the gall bladder, and there was nothing palpable or any tenderness on the right side per rectum. The pre-operative diagnosis was recurrent cholecystitis, but the gall bladder was found to be perfectly normal, and there was a tense mucocele of the appendix. He then completely recovered, went through the war, and was reputed to be well in December, 1919. Possibly the attacks of jaundice were due to disturbance of Meltzer's law of contrary innervation. The sphincter at the lower end of the common bile duct and the muscular fibres of the gall bladder are antagonistic; when the gall bladder contracts the sphincter relaxes; if from reflex disturbance the sphincter fails to relax during contraction of the gall bladder, the pressure of bile in the ducts will rise, and jaundice, and even colic, will result.

Chronic Colitis.

Chronic colitis with exhausting diarrhoea is occasionally due to continued infection from the gall bladder

or appendicitis. This diarrhoea and serious wasting may occur without any localizing symptoms, and with little in the history to suggest the responsible focus. Martin reported one of the first cases of this kind in a man without any signs pointing to appendicitis; exploratory laparotomy showed a thickened appendix with a dilated cavity communicating with the caecum; the appendix contained one or two enteroliths and extremely foul-smelling material, resembling in this respect the motions. Frequent bulky offensive motions with excess of fat occur in chronic pancreatitis, which may result from gall-bladder infection, or from a stone in the common duct.

Glycosuria and Diabetes.

It is now recognized that glycosuria or diabetes, if, indeed, any real distinction between them should be drawn, may be due to pancreatitis set up by infection associated with gall stones. It is not a common sequel, and, though a calculus may get into the common bile duct without obvious symptoms, it must be very rare for gall stones to cause diabetes when their presence is entirely unsuspected. The surgical treatment of certain cases of diabetes practised by Sir A. W. Mayo-Robson is an illustration of preventive surgery, as it aims at the removal of the cause before the resulting pancreatitis has reached an extreme stage.

Cardiac Symptoms.

The dyspepsia due to appendix or gall-bladder disease may be associated with palpitation, irregularity, and substernal distress. M. J. Lichty found that in appendix cases the cardiac disturbance was usually functional only, whereas in gall-bladder disease, either alone or combined with appendicitis, the resulting cardiac disease was more serious. Absorption of toxins from an inflamed gall bladder or ducts may cause myocarditis, anginoid symptoms, and cardiac failure. In a paper on chronic cholecystitis as a cause of myocardial incompetence, Babcock records thirteen cases, medical advice being sought, with two exceptions in which biliary colic occurred, for cardiac disorder without any suspicion of gall-bladder trouble. Angina or anginoid symptoms in patients with gall bladder disease may be due to exhaustion of the poisoned myocardium; a specially interesting case, as it raises the question of Graves's disease as a result of gall-bladder infection, is reported by Sears: a woman had intense precordial pain spreading to the left shoulder, a raised pulse rate, an enlarged thyroid, and other symptoms suggesting Graves's disease; an attack of biliary colic led to operative removal of two gall stones and disappearance of all the symptoms. Babcock described a group of his cases in which attacks of angina preceded cardiac failure. The pain of biliary colic sometimes imitates angina, and cases in which attacks of angina have cleared off after frank biliary colic are on record; it has been suggested that as the result of adhesions the pain of

biliary colic may be felt on the left side. The symptoms of existing valvular disease may be intensified; or compensation may be broken down by toxic myocarditis due to gall-bladder infection. It is important to remember this, and also that the cardiac weakness is often entirely due to the gall-bladder disease, and will be cured by surgical treatment; for operation may be considered to be contraindicated by the condition of the heart. Janeway spoke hopefully of operation in these cases if performed under a local and not a general anaesthetic, the danger being more often from post-anaesthetic pulmonary complications. By waiting time may be lost without improvement in the cardiac condition; but in one case of this kind a vaccine made from organisms isolated from the faeces appeared to do good.

Pyelitis and Pyelonephritis.

Pyelitis and pyelonephritis may be due to infection with *B. coli*, either from the gall bladder or from the appendix; as far as I know, this usually occurs in the right kidney and then suggests a local extension of infection. I have seen right-sided pyelitis in a patient with chronic gall-bladder disease and from the comparative severity of the symptoms suggest acute cholecystitis; the difficulty in such cases is to be sure that both conditions are not present. By becoming adherent to the right ureter an inflamed appendix may cause pyelitis and the aspect of the case may be chiefly renal, and from the free haemorrhage even suggest a calculus; cases of this kind, usually after acute appendicitis, have been described by Hunner. I have been told of a case in which the appendix perforated into the ureter. An inflamed appendix situated high up and close to the kidney may possibly infect the pelvis of the organ.

Synovitis and Arthritis.

In common with other infective conditions of the stomach and intestines, appendicitis and cholecystitis very seldom give rise to a chronic or subacute arthritis such as is associated with oral sepsis. Dysentery is the disease in which the most extensive destruction of mucous membrane and opportunities for absorption occur, and yet synovitis is neither common nor, as a rule, severe. Arthritis in enteric fever is somewhat rare, and might be explained as the result of the early septicaemic stage. It seems plausible to suggest that the liver may protect the joints from damage due to intestinal infections. This hypothesis would naturally at once raise the objection that oral sepsis is an, if not the most, important cause of arthritis, and probably acts by infecting the stomach. On this point I would urge that the discharge of pus from the gums into the mouth, though a frequent cause of gastritis, is not so effective in producing arthritis as infection at the roots causing absorption into the blood stream. In rare instances appendicitis, usually acute, is associated with synovitis; this at first gave rise to the view that inflammation of the appendix, like that of the tonsil, both of which

are rich in lymphoid tissue, was rheumatic in origin. But some years ago Poynton in discussing the association of appendicitis with arthritis came to the conclusion that the articular affection was probably secondary to the appendicitis.

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